## REMARKS

Reconsideration of the instant Office Action, entry of the amendments herein, and withdrawal of the rejection of claims 1-25 are respectfully requested.

In the instant Office Action, claims 1-25 are listed as pending, and claims 1-25 are listed as rejected. Claims 4 and 25 are canceled. Claim 1 is currently amended to recite that the cancer being treated is characterized by an over-expression of peripheral-type benzodiazepine receptor protein. Support for this amendment is found at several locations in the specification: page 1 lines 12-15, page 2 line 20 through page 3 line 2, page 4 lines 5-25, page 5 lines 8-12 and lines 19-23, page 17 lines 3-9 and Figure 7, and page 17 line 30 through page 18 line 21, and Figure 10. Claim 1 is also amended such that the Ginkgo extract contains Ginkgolide B. Support for this amendment is found in the specification on page 10 lines 16-24. Claim 7 is amended to correct for antecedent basis. Claim 21 is amended such that the Ginkgo extract contains Ginkgolide B, supported as for the amendment to claim 1. New claim 26 is submitted. Support for new claim 26 is found in originally filed claims 1 and 25 in combination with the support cited for the amendments to claim 1, *supra*. More specifically, the text of new claim 26 has been drafted to mirror closely the scope of (now amended) claim 1. Applicants submit that the amendments to the claims do not introduce new subject matter and that all amendments are fully supported in the specification.

Applicants are grateful for the April 15, 2005 teleconference which the Examiner granted to Applicants' representatives, Attorney Brian Morrill and the undersigned. The following points were discussed during said teleconference. The Examiner was of the opinion that the specification lacked *in vivo* data in support of the treatment of a patient as recited in claim 1. The Examiner also alleged that the animal model presented by the Applicants (see the specification at page 15 lines 16-26, page 17 line 30 through page 18 line 21, and Figures 10 and 11) described a rat tumor grafted into a mouse host. The Examiner questioned the presence of peripheral-type benzodiazepine receptor protein (PBR) in various types of cells and tumors, in both human and other mammalian organisms. Finally, the Examiner alleged that the terms "cancer" and "extract" appearing in then pending claim 1 were broad terms in the art, therefore the subject matter of claim 1 encompassed the treatment of <u>all</u> cancers with <u>any</u> Ginkgo biloba extract.

In response to these allegations, Applicants' representatives directed the Examiner to the specification. To address the Examiner's question regarding *in vivo* data with respect to human cancer cells, Applicants' representatives directed the Examiner to the text of the specification beginning at page 17, line 30 through page 18, line 21, and to Figures 10 and 11, in which *in vivo* data are presented both with respect to the effects of a Ginkgo biloba extract containing GKB and with respect to the effects of isolated GKB on the proliferation of human breast cancer cells grafted into a mouse host. Additionally, Applicants' representatives directed the Examiner to several *in vitro* studies disclosed in the application, which demonstrate methods to measure PBR protein levels (page 13 line 21 through page 14 line 3) and PBR RNA levels (page 14 lines 4-17), and to perform nucleic acid binding assays (page 14 lines 18-33), cellular proliferation assays (page 15 lines 1-8), and oxidative stress assays (page 15 lines 9-15) to determine the response of a cell to application of a Ginkgo extract. To address the Examiner's question regarding the presence or absence of PBR in cells and tumor cells, Applicants' representatives directed the Examiner to the text of the specification beginning at page 2 line 20 and continuing to page 4 line 4, which discusses PBR, both in normal cells and in a variety of tumors, noting that PBR expression levels were elevated in cancerous cells relative to normal cells. To address the Examiner's concern that claims 1-3 might be interpreted to encompass the treatment of all cancers with any Ginkgo biloba extract, Applicants' representatives suggested that claim 1 might be amended to clarify that the claimed method only encompasses treatment of a cancer characterized by an over-expression of peripheral-type benzodiazepine receptor and, further, that a Ginkgo biloba extract useful for practicing the claimed invention is characterized as containing Ginkgolide B (GKB). Specific wording of such amendments was not discussed.

As per page 2 of the instant Office Action, Applicants note that the Examiner acknowledges Applicants' response to the election requirement of September 24, 2004. Applicants are grateful for the removal of the previous election requirement and Examiner's note that all claims are now considered as drawn to a method of treating cancer.

**1. Claim Rejections – 35 U.S.C. § 112, First Paragraph**

*A) Rejection of claims 1-25 under 35 U.S.C. § 112, first paragraph*

On pages 2-3 of the instant Office action, the Examiner rejects claims 1-25 under 35 U.S.C. § 112, first paragraph, for lack of enablement. More specifically, on page 2 of the instant Office Action the Examiner alleges that the specification,

> "while being enabling for *in vitro* inhibition of MDA-231 cells by Ginkgolide B, does not reasonably provide enablement for the generic 'a method of combating cancer by Ginkgolide B or Ginkgo biloba extracts'."

Beginning on page 2 and continuing to page 3 of the instant Office Action, the Examiner further alleges that:

> "Just because a specific component is effective in the expression of a specific gene or effective in *in vitro* inhibition of a specific cancer cell cultures, one cannot draw a conclusion that either an extract containing that specific compound or the specific compound itself is effective in the *in vivo* treatment of various cancers. Instant specification lacks adequate description to come to that conclusion."

The Examiner goes on to conclude that:

> "Broad claims must have broad basis for support in the specification. In the absence of such support, claims must be limited to the *in vitro* effectiveness of Ginkgolide B in inhibiting MDA-231 cells in culture."

*B) 35 U.S.C. § 112, first paragraph*

The following is a quotation of the appropriate paragraph of 35 U.S.C. § 112 appearing on page 2 of the instant Office Action that forms the basis for the rejection under this section:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set fort the best mode contemplated by the inventor of carrying out his invention."

*C) Cancelled claims*

Applicants note that claims 4 and 25 have been cancelled from the instant application, thus the rejection thereof under 35 U.S.C. § 112, first paragraph, has been obviated.

*D) Claims 1-3 and 5-24 provide enablement under 35 U.S.C. § 112*

Applicants respectfully submit that the Examiner has not demonstrated which portion of the method of claims 1-3 and 5-24 is not fully enabled by or exceeds the disclosure of the instant application. Applicants submit that the description in the specification provides ample disclosure such that one skilled in the art would be able to 1) determine whether the cancer exhibits a deregulation in the expression of proteins (see Nucleic Acid Arrays, page 14 lines 18-33); 2) determine whether the cancer is characterized by over-expression of PBR (see Radioligand Binding Assays, page 13 lines 21-32; Protein Measurement, page 14 lines 1-3; RNA (Northern) Analysis, page 14 lines 4-17 as well as page 11 lines 5-17; Immunocytochemistry of MDA-231 tumors, page 15 line 27 through page 16 line 5); and 3) prepare and administer an effective amount of isolated GKB or a Ginkgo extract containing GKB (see page 1 line 19 continuing through page 2 line 13, and page 10 lines 8- 26).

Applicants further note that the specification, beginning at page 2 line 20 through page 3 line 2, discloses that a number of cancers were already known to express elevated levels of PBR. Applicants further submit that the data presented in Figures 1-11 provide additional important teachings in support of the types of results that the skilled artisan may obtain using the methods and techniques described in the instant application. Applicants respectfully submit that, as discussed herein, the disclosure of the instant application fully enables the skilled artisan as to how to combat cancer according to the claimed method.

Not withstanding the foregoing, and without conceding the correctness of the rejection of claims 1-25 under 35 U.S.C § 112, first paragraph, but rather in an effort to further the application toward allowance, Applicants have amended the claims to clarify that the claimed invention relates to only the treatment of a certain, identifiable class of

cancers characterized by an over-expression of peripheral-type benzodiazepine receptor protein, as follows:

> 1. A method of combating cancer in a patient in need of such combating, wherein the cancer is caused by the deregulation of expression of proteins having a role in regulating tumor cells and wherein said cancer is characterized by an over-expression of peripheral-type benzodiazepine receptor protein, which comprises administering an effective amount of a Ginkgo biloba extract containing Ginkgolide B or isolated Ginkgolide B to said patient.

Applicants further note that claims 2, 3 and 5-24 all depend, directly or indirectly, from newly amended claim 1.

*E) Claims 1-3 and 5-24 provide adequate written description under 35 U.S.C. § 112*

Applicants respectfully submit that while the rejection is couched in terms of enablement, it appears that the Examiner's arguments are also directed to written description. Applicants first respectfully submit that the claimed invention is not, as alleged by the Examiner on pages 2 and 3 of the instant Office Action, directed to the broad treatment of any cancer with any Ginkgo extract, but rather to a method of treating a particular, identifiable class of cancers, (*i.e.,* tumor cells over-expressing PBR) with a specific type of Ginkgo extract, (*i.e.,* a Ginkgo extract containing GKB or isolated GKB).

Applicants note that cancer types characterized by an over-expression of PBR comprise an identifiable, narrow subset of tumors recognized in the art. Applicants direct the Examiner to the disclosure in the specification beginning at page 2 line 20 and continuing through page 3 line 2, wherein a number of references describing mammalian, including human, tumor types which are characterized by high levels of PBR are presented. The teachings of said references may be summarized as follows: Katz *et al.* (Eur. J. Pharmacol., 148:483-484, 1988) disclose that peripheral-type benzodiazepine binding sites are present in the normal human colon and that there is a dramatic increase in the number of peripheral-type benzodiazepine binding sites in adenocarcinoma of the colon. In human ovaries, Katz *et al.* (Clinical Sci., 78:155-158, 1990) report a 3 to 5-fold increase in peripheral-type benzodiazepine binding sites in preparations of ovarian carcinomas as compared to benign ovarian tumors and normal tissues. In a study of human brain tumors (Cornu *et al.*, Acta Neurochir., 199:146-1521992), up to a 12-fold

increase in peripheral-type benzodiazepine binding site densities was observed in high grade astrocytoma and glioblastoma specimens while only a 2 to 3 fold increase was observed in low grade astrocytomas and meningiomas. Cornu *et al.* further showed that metastases of lung or kidney origin were characterized by up to a 20-fold increase in binding site densities as compared to normal brain parenchyma. Miettinen *et al.* (Cancer Research, 55:2691-2695, 1995) showed that PBR was prominently expressed in neoplastic human brain and was low or undetectable in normal brain. Broaddus *et al.* (Brain Research, Vol. 518:199-208, 1990) and Pappata *et al.* (J. Nuclear Med., 32:1608-1610, 1991) report that PBR concentrations were significantly greater in human glioblastoma specimens as compared to normal human frontal cortex samples. Papadopoulos *et al.* (U.S. Application Serial No. 09/047,652, now U.S. Patent Publication 2003/0157095, cited in the specification at page 4, lines 19-21) and Hardwick *et al.* (Cancer Res., 1999, 59:831-842, cited in the specification at page 14 line 6) show a correlation between the aggressiveness of breast cancer cell lines and increased expression of PBR, as well as biopsy data showing that aggressive breast carcinomas exhibit very high levels of PBR as compared to *in situ* and invasive breast carcinomas, and to normal breast tissue. Copies of the foregoing references are submitted in an IDS filed herewith.

Applicants submit that what was not known in the art was that cancers characterized by abnormally high or low levels of PBR would respond differently to, and are particularly amendable to treatment using isolated GKB or a Ginkgo biloba extract containing GKB. In the instant application, Applicants teach, with support from both *in vitro* and *in vivo* studies, that tumors characterized by abnormally high levels of PBR, *e.g.*, MDA-231 cells, are significantly more responsive to treatment with isolated GKB or a Ginkgo extract containing GKB than are tumors which are not characterized by abnormally high levels of PBR, *e.g.*, MCF-7 cells.

On pages 2-3 of the instant Office action, the Examiner alleges that the instant application supports only *in vitro* inhibition of MDA-231 cells using GKB. Applicants respectfully disagree and direct the Examiner to disclosure in the specification beginning at page 17 line 30 and continuing to page 18 line 21 and to Figures 10 and 11, wherein the Applicants present *in vivo* data demonstrating the efficacy of a Ginkgo biloba extract

containing GKB (EGB 761®) and of GKB alone against MDA-231 cells, an aggressive type of human breast cancer which expresses an abnormally high level of PBR, as compared to other less aggressive types of human breast cancer, such as MCF-7 (see page 12 lines 18-22, and U.S. Patent Publication 2003/0157095, *supra*). Applicants have found that MDA-231 cells express approximately 60-fold more PBR than the MCF-7 cells (see page 12 lines 20-22). Briefly, MDA-231 xenografts in nude mice were prepared and treated with either EGB 761® or GKB and growth of the xenografts was monitored. As shown in Figure 10 and discussed in the specification on page 18 lines 1-3, treatment with EGB 761® and with GKB resulted in a 35% and a 32% decrease in tumor size, respectively. As shown in Figure 11, especially 11E to 11H, and discussed in the specification on page 18 lines 4-21, treatment with EGB 761® and with GKB reduced the nuclear expression of PBR protein present in cells taken from the middle of tumors growing in mice.

Elevated expression of PBR is a distinguishable and testable attribute of cancer cells which, as Applicants demonstrate in the instant application, respond differently to treatment with Ginkgo extracts. Applicants submit that the instant application allows the skilled artisan to select patients who would be amendable to treatment according to the method of claims 1-3 and 5-24, that is 1) to determine whether cancerous cells express high levels of PBR, and 2) to apply or administer a Ginkgo extract containing GKB, or an extract of GKB alone, to a patient in whom such cancerous cells are present.

As noted above, without conceding to the correctness of the Examiner's rejection, and in an effort to advance the prosecution of the instant application to allowance, Applicants have amended the claims to further clarify that the claimed invention relates to only the treatment of a certain, identifiable class of cancers characterized by an over-expression of peripheral-type benzodiazepine receptor protein.

*F) Request for withdrawal of rejection of claims 1-3 and 5-24 under 35 U.S.C. § 112, first paragraph*

Applicants respectfully submit that the disclosure of the instant application fully teaches the skilled artisan how to practice all elements of the claimed method and thus fulfills the enablement requirement of 35 U.S.C. § 112, first paragraph. Specifically,

Applicants have taught how to determine whether cancer cells exhibit changes in gene expression, whether the cancer cells over-express PBR and how to administer a Ginkgo extract containing GKB or GKB. Applicants also submit that the disclosure of particular, identifiable cancers characterized by high levels of PBR, the teachings of methods to determine if a cancer cell over-expresses PBR, and the data presented in the specification illustrating the effects of EGB 761® and of GKB upon tumors *in vivo* as well as tumor cells *in vitro* fulfills the written description requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully request that the rejection of claims 1-3 and 5-24 under 35 U.S.C. § 112, first paragraph, be withdrawn.

**2. Claim Rejections – 35 U.S.C. § 102(b) and 102(e)**

*A) Rejection of claims 1-25 under 35 U.S.C. § 102(b) and 102(e)*

On pages 3-4 of the instant Office action, the Examiner rejects claims 1-25 under 35 U.S.C. § 102(b) as anticipated by DE 42 08 868 (referred to hereinafter as the "DE '868" reference) and by EP 0 359 951 (referred to hereinafter as the "EP '951" reference). On page 4 of the instant Office action, the Examiner rejects claims 1-25 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 6,316,690 to Fogarty (referred to hereinafter as "Fogarty").

On page 3 of the instant Office Action, the Examiner alleges that DE '868 and EP '951 each discloses a method of treatment of cancer using Ginkgo biloba extracts. The Examiner also alleges on page 3 that "the mechanism by which the composition of the prior art functions has no patentable significance since it is the inherent effect of the prior art extract." The Examiner notes, however, that the rejections over DE '868 and EP '951 may be reconsidered in light of full translations. As such, full translations of the DE '868 and EP '951 documents are provided in an IDS filed herewith. On page 4 of the instant Office Action, the Examiner states that Fogarty discloses the anti-tumor activity of Ginkgo biloba extract against a variety of tumors.

*B) 35 U.S.C. § 102(b) and 102(e)*

The following are quotations of the appropriate paragraphs of 35 U.S.C. § 102(b) and 102(e) that form the basis for the rejection under this section. As pointed out by the Examiner on page 3:

> 35 U.S.C. § 102(e) The invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treated defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The quote for 35 U.S.C. § 102(b), however, is lacking in the instant Office Action. Applicants presume that the Examiner intended to include the following:

> 35 U.S.C. § 102(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the applicant for patent in the United States, or

*C) Cancelled claims*

Applicants note that claims 4 and 25 have been cancelled from the instant application, thus the rejection thereof under 35 U.S.C. § 102(b) and 102(e) has been obviated.

*D) Claims 1-3 and 5-24 are not anticipated under 35 U.S.C. § 102(b) and 102(e) by DE 42 08 868, EP 0 359 951 nor US 6,316,690*

Applicants respectfully disagree with the Examiner's allegation that references DE '868 and EP '951 anticipate the claimed invention under 35 U.S.C. § 102(b) and that Fogarty anticipates the claimed invention under 35 U.S.C. §102(e), because each of DE '868, EP '951 and Fogarty fail to teach or suggest all of the limitations of claim 1, much less the additional limitations present in claims 2, 3 and 5-24 even prior to the present amendments. Notwithstanding the deficiencies of the teachings of DE '868, EP '951 and

Fogarty, and without conceding the correctness of the Examiner's rejection based thereon, Applicants have now amended claim 1, and as such, claims 2, 3 and 5-24 which depend either directly or indirectly from claim 1, to clarify that the cancer cells subject to treatment with a Ginkgo biloba extract containing GKB or with isolated GKB are those which exhibit elevated expression of PBR. Applicants respectfully submit that neither DE '868, EP '951 nor Fogarty teach that, of all cancers, those which exhibit elevated levels of PBR are particularly amendable to treatment using a Ginkgo biloba extract containing GKB or with isolated GKB.

Regarding EP '951, Applicants submit that EP '951 teaches the usefulness of using a dry extract of Ginkgo biloba in conjunction with traditional cancer treatments (see claim 1 and also column 1, paragraph 5 therein). Indeed, the single Example provided in EP '951 (column 2) describes administering a Ginkgo extract to patients already being treated with Epirubincin cyclophosphamide, or Leucoverin and Fluorouracil. At column 1, paragraph 6 of the specification, EP '951 teaches that "chemotherapeutic agents in connection with ginkgoflavonglycosides show a greater cancer growth–inhibiting effect than the combined application of various cytostatic agents alone." At column 1, paragraph 7 of the specification, EP '951 teaches that "ginkgo extracts cause a potentiating effect in the cancer growth-inhibiting effect of various cytostatic agents." Applicants respectfully submit that EP '951 does not teach or suggest that ginkgoflavonglycosides actually exhibit anti-cancer activity, nor that it is the ginkgoflavonglycoside component of the treatment which is efficacious against the cancer. Applicants submit that EP '951 only teaches that cytostatic agents may exhibit greater efficacy in combination with ginkgoflavonglycosides.

Regarding DE '868, claim 1 thereof recites use of a drug "characterized by the fact that the drug contains ginkgolides as the active ingredient." In column 1, paragraph 7, DE '868 stresses that "it is of importance that the ginkgolides are administered before the dose of the chemotherapeutic agents." (emphasis added) Furthermore, in column 1, paragraph 7 of the specification DE '868 recites that "a particularly high amplification of the tumor growth-inhibiting effect of cytostatic chemotherapeutic agents can be achieved by multiple prior administrations of ginkgolides." In column 1, paragraph 8 of the specification DE '868 discloses that "in the case of existing resistance to cytostatic agents

the prior administration of ginkgolide leads to a renewed response to the cytostatic agent." In column 1, paragraph 9 of the specification DE '868 discloses that

> "Ginkgolide B leads to characteristic changes in form of the membrane of the human red blood cell. It has still not been made clear whether membrane effects of this type are also to be observed in the tumor cell and whether these are responsible for the effect of amplifying the chemotherapy."

Applicants submit that that DE '868 teaches the skilled artisan only that ginkgolides amplify the effect of cytostatic agents. Applicants submit that the inventors of DE '868 are unsure as to how the Ginkgolide may be achieving this amplifying effect and, as such, DE '868 does not and cannot teach or suggest that the Ginkgolide exhibits anti-cancer activity observed when administered in combination with cytostatic agents.

Lastly, and quite significantly, Applicants submit that references DE '868 and EP '951 both fail to teach or suggest that over-expression of PBR is a distinguishable and testable attribute of cancer cells that may be used to determine which patients may be most amendable to treatment with a Ginkgo extract containing GKB or with isolated GKB.

Further to his rejection over DE '868 and EP '951 on page 3 of the instant Office Action, the Examiner also states that "the mechanism by which the composition of the prior art functions has no patentable significance since it is the inherent effect of the prior art extract." Applicants are uncertain as to the intent of the Examiner's comment, however, Applicants respectfully submit that the method of the instant invention is not drawn to the mechanism of cancer progression. Rather the claimed (as amended) invention is drawn to a method to combat cancer by determining if a cancer is characterized by an over-expression of PBR and administering a Ginkgo biloba extract containing GKB or isolated GKB. An essential teaching of Applicants' invention is that cancers characterized by high levels of PBR are more amenable to treatment with a Ginkgo biloba extract containing GKB or isolated GKB. Neither DE '868 nor EP '951 teach or suggest to the skilled artisan that cancers characterized by over-expression of PBR should be preferentially selected for treatment with a Ginkgo biloba extract containing GKB or isolated GKB.

Regarding Fogarty, on page 4 of the instant Office Action, the Examiner states that Fogarty:

> "discloses the anti-tumor activity of Gingko biloba extract is known in the art. The tumors discussed in specific include hepatic, colon, leukemia, lymphoma, glioma, breast, prostate, pancreas, bladder, melanoma and lung (col. 12, line 44 through col. 13, line 21)."

Applicants note that Fogarty (column 12, lines 44-45) makes the sweeping statement that "a variety of herbs and Chinese medicines have been identified for having anti-tumor activity." However, neither Fogarty itself nor a single reference cited by Fogarty (see *e.g.,* column 12 line 44 through column 13 line 27 therein) recites treatment of cancer with Ginkgo biloba extracts or with isolated GKB. The Abstract of each article cited by Fogarty is submitted in the IDS filed herewith, the teachings of which may be summarized as follows: Zheng *et al.,* (Immunopharmacol. Immunotoxicol., 17:69-79, 1995) disclose use of a root tuber extract; Brochers *et al.,* (Proc. Soc. Exp. Biol. Med., 4:281-93, 1999) disclose the use of various whole mushrooms and isolated compounds; Hu *et al.,* (Planta Med., 62:573-5, 1996) recite compounds from rhizomes; Zheng *et al.,* (J. Cell. Biochem. Suppl., 27:106-12, 1997) disclose the use of garlic and *Rhizoma zedoariae*; Nakahata *et al.,* (Am. J. Chin. Med., 26:311-23, 1998) recite the use of *Scutellariae radix*; Kato *et al.,* (J. Invest. Dermatol., 111:640-4, 1998), Huang *et al.,* (Keio J. Med., 46:132-7, 1997), Yamashiki *et al.,* (J. Gastroenterol. Hepatol., 11:137-42), Sakamoto *et al.,* (Am. J. Chin. Med., 22:43-50, 1994), and Ito *et al.,* (Jpn. J. Pharmacol., 41:307-14, 1986) teach the use of Sho-saiko-to and /or Juzen-taiho-to which are popular herbal medicines in Japan; Michaud *et al.,* (J. Natl. Cancer Inst., 91:605-13, 1999) disclose "fruit and vegetable" intake; Sasaki *et al.,* (Nutr. Cancer, 33:76-81, 1999) teach isothiocyanates "found in human diets"; and Sengupta *et al.,* (Eur. J. Cancer Prev., 8:325-30, 1999) disclose the use of lycopene from tomato. Applicants respectfully submit that a skilled artisan would not consider any of these references, either alone or in any combination, as supporting Fogarty's broad statement that the anti-tumor activity of a Ginkgo biloba extract is known.

Moreover, in Table 2 Fogarty presents a laundry list of "extracts of herbs and Chinese medicines that are known to have antitumor activity in mammals." Considering that none of the references listed by Fogarty recite the use of a Ginkgo extract, Applicants

submit that Fogarty presents no teaching that would even allow, much less direct, one to know which extract in Table 2 might have an effect on which, if any, of the tumors listed in column 12 line 44 and following, let alone which, if any, of the tumors are affected by application of Ginkgo biloba. Applicants submit that Fogarty, at best, suggests in a vague way the anti-tumor activity of the extracts of Table 2 only when the tumor is artificially induced by a v-myb gene in transgenic *Drosophila* larvae. More importantly, Fogarty does not teach or suggest that tumor cells over-expressing PBR should be preferentially selected for treatment with a Ginkgo biloba extract containing GKB or with isolated GKB.

Applicants further submit that, not only do DE '868, EP '951 and Fogarty fail to teach or suggest to the skilled artisan to use a Ginkgo extract containing GKB or GKB to combat cancer cells characterized by an over-expression of PBR (claim 1), these references also fail to teach or suggest to the skilled artisan to combat cancer characterized by an over-expression of PBR:

a) in which a deregulation of protein expression (as per claim 2) or an over-expression of proteins (as per claim 3) having a role in regulating tumor cells results in the proliferation of cancer cells, where the treatment combats the proliferation of the cancer cells;

b) in which the proliferation of cells is caused by the over-expression of oncogenes (as per claim 5), particularly where the oncogenes are one or more of APC, PE-1, RhoA and c-Jun (as per claim 6), where the treatment combats the proliferation of cancer cells;

c) in which the deregulation of the expression of proteins results in cancer cells expressing an abnormal level of PBR, where the treatment results in decreasing the expression of PBR in the cancer cells (claim 7);

d) in which the cancer is human breast cancer cells (claim 8), glioblastomas (claim 9), human brain tumor cells (claim 10), human astrocytoma cells (claim 11), human colonic carcinoma cells (claim 12), human colonic adenocarcinoma cells (claim 13), human ovarian carcinoma cells (14), or human hepatocellular carcinoma cells (claim 15);

e) by decreasing the expression of PBR by decreasing the expression of PBR mRNA in the cancer cells (as per claim 16); and

f) where the cancer is caused by a deregulation in of the expression of proteins resulting in increasing the expression of a c-Myc protooncogene (claim 17), or decreasing the expression of genes APC, PE-1, RhoA, c-Jun, prothymosin-α, CDK2, p55CDC, myeloblastin, p120 proliferating-cell nuclear antigen, NET1, ERK2, Adenosine A2A Receptor, Flt3 ligand, Grb2, Clusterin, RXR-β, Glutathione S-transferase P, N-Myc, TRADD, SGP-2, NIP-1, Id-2, ATF-4, ETR-101, ETR-103, macrophage colony-stimulating factor-1, heparin-binding EGF-like growth factor, hepatocyte growth factor-like protein, inhibin α, CD19 B-lymphocyte antigen, L1CAM, β-catenin, and integrin subunits α3, α4, α6, β5, and αM (claims 18-24).

Applicants further submit that DE '868, EP '951 and Fogarty also fail to teach or suggest to the skilled artisan how to prepare a pharmaceutical composition comprising an effective amount of a Ginkgo biloba extract containing GKB or isolated GKB useful for combating cancer characterized by an over-expression of PBR (new claim 26).

*E) Request for withdrawal of rejection of claims 1-3 and 5-24 under 35 U.S.C. § 102(b) and 102(e)*

Applicants respectfully request that the anticipation rejections of claims 1-3 and 5-24 under 35 U.S.C. § 102(b) over DE '868, EP '951, and the anticipation rejections of claims 1-3 and 5-24 under 35 U.S.C. § 102(e) over Fogarty, each be withdrawn.

**3. Claim Rejections – 35 U.S.C. § 103(a)**

*A) Rejection of claims 1-25 under 35 U.S.C. § 103(a)*

On page 4 of the instant Office action, the Examiner rejects claims 1-25 under 35 U.S.C. § 103 as obvious over U.S. Patent No. 6,316,690 (Fogarty). Fogarty employs an artificial system in which transgenic *Drosophila* genetically engineered to express a v-myb transgene are treated with uncharacterized extracts of "Chinese herbs" to delay tumor progression in transgenic fly larva.

*B) 35 U.S.C. § 103(a)*

The following is a quotation of the appropriate paragraph of 35 U.S.C. § 103(a) appearing on page 4 of the instant Office Action that forms the basis for the rejection under this section:

> 35 U.S.C. § 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

*C) Cancelled claims*

Applicants note that claims 4 and 25 have been cancelled from the instant application, thus the rejection thereof under 35 U.S.C. § 103(a) has been obviated.

*D) Claims 1-3 and 5-24 are not obvious under 35 U.S.C. § 103(a) over US 6,316,690*

Applicants respectfully submit that the Examiner has not made a prima facie case for obviousness. *In re Vaeck* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) states that there are three basic criteria to be met to establish a prima facie case of obviousness: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, 2) there must be a reasonable expectation of success and 3) the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Fogarty, column 3 lines 35-38 states that "a critical feature" of the subject animals is that they are transgenic for a particular gene which is "spatially expressed in a manner sufficient to result in the desired neoplastic phenotype." Fogarty provides no evidence that the teachings of their model system function in a similar manner when the tumor, in any organism, lacks this critical transgenic feature. Fogarty does not teach or suggest that tumor cells may be characterized by an over-expression of PBR, let alone teach or suggest that a Ginkgo extract would be more effective against tumor cells which over-express PBR protein than tumor cells which do not.

*E) Request for withdrawal of rejection of claims 1-3 and 5-24 under 35 U.S.C. § 103(a)*

As Fogarty fails to teach or suggest all of the claim limitations, Applicants respectfully request that the rejection of claims 1-3 and 5-24 under 35 U.S.C. § 103(a) over Fogarty be withdrawn.

Applicants believe that the claims as amended are in a condition for allowance. Reconsideration of the instant Office Action, entry of the amendments submitted herewith, and allowance of all pending claims are respectfully requested. Prompt and favorable action is solicited.

Respectfully submitted,

Date:
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